REMARKS

The presently claimed invention features methods for reducing immune-mediated damage to cells, tissues or organs by contacting the cells, tissues or organs with a polypeptide comprising all or an AVLSAEQLR (SEQ ID NO:3) containing polypeptide fragment of human Hsp47 (SEQ ID NO:6). Studies described in the present specification demonstrate an that a polypeptide consisting of human Hsp47 fused to GST protected mice from graft versus host disease, fur ruffling, weight loss and death following a bone marrow transplant. Moreover, polypeptides comprising various portions of human Hsp47 comprising the amino acid sequence AVLSAEQLR and a polypeptide consisting of human Hsp47 fused to GST protect endothelial cells from CIK-mediated lysis (pages 44-45 of the specification).

Rejections Under 35 U.S.C. §112 first paragraph (enablement)

The Examiner rejected claims 1-15 under 35 U.S.C. §112, first paragraph as allegedly not enabled. The Examiner argued that the specification, "while being enabling for a method of reducing immune mediated damage to cells, tissues or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of HSP47 (SEQ ID NO:6) or a fragment thereof that consists of AVLSAEQLR (SEQ ID NO:3)" or one of the three disclosed deletion mutants, the specification "does not reasonably provide enablement for the broader recitation of reducing immune mediated damage to a cell, tissue or organ comprising contact with any HSP47 related immunoprotective polypeptide, or with a composition comprising any HSP47 or any fragment or any variant thereof."

Claims 1-15 have been cancelled, and claims 43-57 have been added. The newly added claims are drawn to methods for reducing an immune-mediated damage to cells, tissue or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of a polypeptide that includes at least a polypeptide fragment of human Hsp47 (SEQ ID NO:6) that includes the sequence AVLSAEQLR (SEQ ID NO:3).

The Examiner stated that the specification does not enable one to make or use a polypeptide comprising SEQ ID NO:3. The Examiner stated that "by reciting the term

'comprises' in the instant claims, said polypeptide can also encompass an indeterminate number and type of additional amino acids, in addition to the amino acids in the recited SEQ ID NOs." The Examine then went on to argue that it was unpredictable whether amino acids could be added while still retaining activity.

Applicant believes that the results described in the specification demonstrate that a range of additional amino acids can be added to SEQ ID NO:3 or SEQ ID NO:6 while retaining activity. For example, the Examiner has concluded that the specification enables claims drawn to the use of human Hsp47, deletion mutant 1, deletion mutant 2, and deletion mutant 3. All of these polypeptides are polypeptides that comprise SEQ ID NO:3. Thus, it is clear that a polypeptide comprising SEQ ID NO:3 (AVLSAEQLR) can retain activity. Moreover, the specification describes the results of an experiment in which irradiated mice were administered bone marrow cells and spleen derived stem cells exposed to either a human Hsp47-GST fusion protein or GST control. The mice were monitored for four weeks after the bone marrow transplant. All five mice receiving the human Hsp47-GST fusion protein treatment were protected from the onset of graft versus host disease, fur ruffling, weight loss and death. All five mice treated with GST exhibited signs of graft versus host disease, fur ruffling, weight loss following a bone marrow transplantation, and four of these five mice died. Thus, it is clear that a polypeptide comprising SEQ ID NO:6 (human Hsp47) fused to a heterologous protein can retain activity. In view of these teachings, it is Applicant's position that the present claims are enabled.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright,* 999 F.2d 1510 (Fed. Cir. 1993). The Examiner cited Seebach et al. (*Nat. Immun.* 15:176, 1996-97) to support the assertion that SEQ ID NO:3 displays "different activity depending on whether it is present in an Hsp47 polypeptide as disclosed by the instant specification, or in an HLA molecule as taught by Seebach et al." However, it is not clear to the Applicant that the HLA molecules described by Seebach et al. as being unable to protect cells from NK cell-mediated lysis include SEQ ID NO:3. First, Seebach et al. does not provide the sequences of the HLA molecules used. Second,

Figure 2 of the present specification provides an alignment of SEQ ID NO:3 with portions of several HLA molecules. Each of the HLA molecules includes the sequence AAHVAEQLR. This sequence differs from that of SEQ ID NO:3 at three positions. Whether or not Seebach et al. properly examined protection from immune-mediated damage, it is not at all clear that Seebach et al.'s studies involved the use of an HLA molecule comprising SEQ ID NO:3. Nothing in either Seebach et al. or the present application indicates that this is the case. Thus, Applicant does not believe that the Office has met the initial burden of providing a "reasonable explanation as to why it believes that the scope of protection" of the present claims "is not adequately enabled by the description of the invention provided in the specification of the application." Moreover, Applicant has provided the results of studies showing that polypeptides comprising SEQ ID NO:3 or SEQ ID NO:6 retain activity even when additional amino acids are present. It is Applicant's position that the present claims are fully enabled, and Applicant respectfully requests that the Examiner withdraw the rejection under the enablement requirement of 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected previously pending claims 1-15 under 35 U.S.C. §112, first paragraph as allegedly not supported by an adequate written description. Claims 1-15 have been cancelled. Claims 43-57 have been added. It is Applicant's position that the present claims meet the written description requirement of 35 U.S.C. §112, first paragraph.

The Examiner argued that claims drawn to the use of a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or comprising the amino acid sequence of SEQ ID NO:6 fail to meet the written description requirement because the "polypeptide can also encompass an indeterminate number and type of additional amino acids in addition to the amino acids in the recited SEQ ID NOs."

Claims 43, 45 and 47 do not include the comprising language objected to by the Examiner. Thus, claim 43 is drawn to the use of a polypeptide "consisting of the amino acid sequence of a polypeptide fragment of SEQ ID NO:6, the polypeptide fragment comprising the amino acid sequence AVLSAEQLR (SEQ ID NO:3)." Thus, the sequence of all of possible polypeptides encompassed by this claim are disclosed in the present specification. Claim 45 is

drawn to a polypeptide "consisting essentially of a polypeptide having the amino acid sequence of a polypeptide fragment of SEQ ID NO:6, the polypeptide fragment of SEQ ID NO:6 comprising the amino acid sequence AVLSAEQLR (SEQ ID NO:3)." Claim 47 is drawn to "a polypeptide consisting essentially of the amino acid sequence AVLSAEQLR (SEQ ID NO:3)." It is believed that all of these claims meet the written description requirement.

Claims 43 and 46 are drawn to polypeptides comprising a specified sequence. These claims also meet the written description requirement. Those skilled in the art can readily identify additional amino acids which could flank the recited amino acid sequences. Moreover, these claims set forth a structural feature that is common to the polypeptides employed in the claimed methods. This common structural feature is the amino acid sequence AVLSAEQLR. Applicants have exemplified a number of polypeptides which include this common structural feature, including Hsp47 and deletion mutants 1, 2, and 3. The data presented in the specification demonstrate that these polypeptides having the common structural feature can all act as an immunoprotective agent. Accordingly, it is Applicant's position that claims 43 and 46 meet the written description requirement.

In view of the forgoing, Applicant respectfully requests that the Examiner withdraw the rejections based on the written description requirement of 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected previously pending claims 6 and 13 under 35 U.S.C. §112, first paragraph as allegedly indefinite. Claims 6 and 13 have been cancelled, obviating this rejection.

Objections to the Specification

The Examiner objected to the specification due to the presence of a typographical error and a hyperlink. Applicant has amended the specification to address these objections.

Conclusion

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for excess claim fees and a Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 16 JAN 2002

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 10, line 4, has been amended as follows:

"Percent (%) amino acid sequence identity" with respect to the Hsp47 polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the wild-type human Hsp47 sequence (see Figure 1A), after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. "Percent (%) nucleotide sequence identity" with respect to the Hsp47 polypeptide-encoding sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotide sequence shown in Figure 1, after aligning the sequences an introducing gaps, if necessary, to achieve the maximum percent sequence identity. The % identity values used herein are generated by WU-BLAST-2 which was obtained from [[Altschul *et al., Methods in Enzymology, 266*:460-480 (1996):http://blast.wustl/edu/blast/README.html]] (Altschul et al., *Methods in Enzymology*, 266:460-480 (1996); available on the internet at blast.wustl/edu/blast/README.html. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span =1, overlap fraction = 0.125, word threshold (T) = 11. The HSP S and HSP S2 paramaters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity. A % amino acid sequence identity value is determined by the number of matching identical residues divided by the total number of residues of the "longer" sequence in the aligned region. The "longer" sequence is the one having the most actual residues in the aligned region (gaps introduced by WU-Blast-2 to maximize the alignment score are ignored).

Paragraph beginning at page 20, line 28, has been amended as follows:

In general, doses of immunoprotective amounds can be packaged in liquid or solid (*e.g.*, lypphilized) form in appropriate containers such as [viles] vials, *etc.* If liquid, the composition is preferably in a pharmaceutically acceptable medium (carrier). If solid, it should be prepared so that when reformulated as a liquid (*e.g.*, with water or a pharmaceutical carrier) a pharmaceutically acceptable composition is formed.

Paragraph beginning at page 45, line 7, has been amended as follows:

Nucleic acids encoding huHsp47 and fragments were cloned into [eucaryotic] eukaryotic expression vectors. A nucleic acid encoding a fragment of huHsp47, in which the carboxy-terminal RDEL amino acid sequence is deleted, was PCR amplified from the pUC//huHsp47 plasmid using the following primers: 5' primer CGGAATTCTGGCCGAGGTGAAGAAACC, 3' primer AGTTCCCACTGTTCTACGACCTACGACCTAGGGC. The amplified product was ligated to the melittin secretion signal and Kozak sequences derived from pMel-Bac (Invitrogen, San Diego, CA) and the resulting fragment was cloned into the multiple cloning site of pEGFP-N1 (Clontech, Palo Alto, CA) using general techniques well known to those of skill in the art. The resulting plasmid, eGFP-Hsp47, was transfected into EC.

Paragraph beginning at page 55, line 24, has been amended as follows:

EGFP-tagged Hsp47 FACS probe was generated through additional genetic engineering (Figure 8A). This enabled searching for both potential huHsp47 receptors and for CIK subsets expressing such Hsp47 binding proteins. FACS analysis of mature d_{21} CIK with eGFP-tagged HuHsp47 as FACS probe for the FITC channel, with CE56-PE co-staining, is based on differences in the Hsp47 binding [abiligy] ability of the analyzed CIK. The eGFP tagged Hsp47 probe stained a quarter of mature CIK (26%).

In the claims:

Claims 1-15 have been cancelled.